UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/306,986	05/07/99	TRINH	T 0942.4570001

HM22/0102
STERNE KESSLER GOLDSTEIN & FOX PLLC
ATTORNEYS AT LAW
1100 NEW YORK AVENUE NW SUITE 600
WASHINGTON DC 20005-3934

EXAMINER	
HUTSON, R	
ART UNIT	**PAPER NUMBER**
1652	9

DATE MAILED: 01/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/306,986	Trinh et al.
Examiner	**Group Art Unit**
Richard Hutson	1652

☒ Responsive to communication(s) filed on *Oct 19, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-37* is/are pending in the applicat

Of the above, claim(s) *1-7 and 14-37* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *8-13* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4 and 5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-37 are still at issue and are present for examination.

Applicant's election without traverse of Group II, Claims 8-13 in Paper No. 8 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-7 and 14-37 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 contains the trademark/trade name VENT™ and DEEPVENT™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the

goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a species of thermostable DNA polymerase and, accordingly, the identification/description is indefinite.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 9 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 8 wherein said peptide or polypeptide having ribonuclease activity is selected from the group consisting of RNase A, RNase T1, RNase H, RNase S, RNase B, RNase C, RNase T2 or enzymatically active fragments thereof, does not reasonably provide enablement for the method of claim 8 wherein said peptide or polypeptide having ribonuclease activity is selected from the group consisting of fragments, variants, derivatives or mutants of those RNases listed in claim 9. Further the specification, while being enabling for the method of claim 11 wherein said thermostable DNA polymerase is selected from the group consisting of *Taq* DNA polymerase, *Tne* DNA polymerase, *Tma* DNA polymerase, *Tth* DNA polymerase, *Tli* or VENT™ DNA polymerase, *Pfu* DNA polymerase, DEEP VENT™ DNA polymerase, *Pwo* DNA polymerase, *Bst* DNA polymerase, *Bca* DNA polymerase, *Tfl* DNA polymerase, or enzymatically active fragments thereof, does not reasonably provide enablement for the method of claim 11 wherein said thermostable DNA polymerase is selected from the

group consisting of fragments, variants, derivatives or mutants of those thermostable DNA polymerases listed in claim 12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The basis of this rejection is that a method cannot be enabled if those products used by the method are not enabled.

Claims 9 and 12 are so broad as to encompass any method of claim 8 wherein said method comprises using any of fragments, variants, derivatives or mutants of those RNases and thermostable DNA polymerases listed in claims 9 and 12 respectively. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of ribonuclease and thermostable DNA polymerase enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the described method using known or naturally occurring ribonuclease and thermostable DNA polymerase proteins.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass methods of use of all modifications and fragments of any ribonuclease or thermostable DNA polymerase because the specification does not establish: (A) regions of the proteins structure which may be modified without effecting their activity; (B) the general tolerance of ribonucleases and thermostable DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims drawn to methods of use of those proteins broadly including any number of amino acid modifications of any ribonuclease and thermostable DNA polymerase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ

19 24 (CCPA 1970)). Without sufficient guidance, determination of those molecules having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

5. Claims 9 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed methods for synthesizing a nucleic acid molecule said method comprising: a) mixing a nucleic acid template, with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and b) incubating said mixture under condition sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template. The specification fails to describe in any fashion the physical and/or chemical properties of the claimed genus of proteins necessary for use in the claimed methods and identifies only those ribonucleases and DNA polymerases listed in claims 9 and 12, respectively as a member of the genus having the necessary functional properties. Moreover, the specification fails to describe any other representative species of ribonuclease or thermostable DNA polymerase by any identifying characteristics or properties other than by function. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and

exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 8-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Maudru et al. (Journal of Virological Methods 66: 247-261, July 1997).

Maudru et al. examine the cause and teach a method for the elimination of background signals in a modified polymerase chain reaction-based reverse transcriptase assay. Maudru et al. teach that the background signal of the PCR-based reverse transcriptase(PBRT) assay was due to an intrinsic RNA-dependent DNA polymerase activity of the Taq DNA polymerase enzyme used for the assay. They further teach that this background signal could be eliminated by inserting a ribonuclease digestion step prior to amplifying the cDNA product of the RT reaction by PCR. Thus Maudru et al. anticipates claims 8-12 drawn to a method for synthesizing a nucleic acid molecule said method comprising: a) mixing a nucleic acid template, with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and b)

incubating said mixture under condition sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template, wherein said ribonuclease activity is selected from the group consisting of fragments, variants, derivatives or mutants of those RNases listed in claim 9, wherein said thermostable DNA polymerase is selected from the group consisting of fragments, variants, derivatives or mutants of those thermostable DNA polymerases listed in claim 12.

7. Claims 8-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Don et al. (Nucleic Acids Research 21(3): page 783, 1993).

Don et al. teach a "one tube reaction" for synthesis and amplification of total cDNA from a small number of cell. Specifically Don et al. teach a method of synthesizing a nucleic acid comprising mixing nucleic acid template, MMLV reverse transcriptase, RNase H, T4 DNA polymerase and *Taq* DNA polymerase. Thus Don et al. anticipates claims 8-12 drawn to a method for synthesizing a nucleic acid molecule said method comprising: a) mixing a nucleic acid template, with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and b) incubating said mixture under condition sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template, wherein said ribonuclease activity is selected from the group consisting of fragments, variants, derivatives or mutants of those RNases listed in claim 9, wherein said thermostable DNA polymerase is selected from the group consisting of fragments, variants, derivatives or mutants of those thermostable DNA polymerases listed in claim 12.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maudru et al. or Don et al.

As discussed above, Maudru et al. examine the cause and teach a method for the elimination of background signals in a modified polymerase chain reaction-based reverse transcriptase assay and Don et al. teach a "one tube reaction" for synthesis and amplification of total cDNA from a small number of cell. One of ordinary skill in the art would have been motivated to use the method of claim 10 to synthesize a nucleic acid molecule wherein one or more of said nucleotides are detectably labeled so that the synthesized DNA molecule could be used as a probe to isolate similar DNA molecules from a DNA library, or so that the label could be used as a means of measuring the amount of DNA synthesized. One would have had a reasonable expectation of success based on the knowledge well known in the art of using radioactive nucleotides in DNA synthesis reactions to detectably label the synthesized product.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on M-F from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy (Murthy), can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Richard Hutson Ph.D.
12/22/2000